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Breastfeeding in Children of Women Taking Antiepileptic Drugs: Cognitive Outcomes at Age 6 Years

Kimford J. Meador, MD, Gus A. Baker, PhD, Nancy Browning, PhD, Morris J. Cohen, EdD, Rebecca L. Bromley, PhD, Jill Clayton-Smith, MD, Laura A. Kalayjian, MD, Andres Kanner, MD, Joyce D. Liporace, MD, Page B. Pennell, MD, Michael Privitera, MD, and David W. Loring, PhD for the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group

Department of Neurology and Neurological Sciences, Stanford University, Stanford, California (Meador); Walton Centre for Neurology and Neurosurgery, University of Liverpool, Merseyside, England (Baker); The EMMES Corporation, Rockville, Maryland (Browning); Departments of Neurology, Pediatrics, and Psychiatry, Georgia Regents University, Augusta (Cohen); Institute of Human Development, University of Manchester, and Central Manchester University Hospitals National Health Service Foundation Trust, Manchester, England (Bromley, Clayton-Smith); Department of Neurology, University of Southern California, Los Angeles (Kalayjian); Department of Neurology, University of Miami, Miami, Florida (Kanner); Department of Neurology, Riddle Health Care, Media, Pennsylvania (Liporace); Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts (Pennell); Department of Neurology, University of Cincinnati, Cincinnati, Ohio (Privitera); Departments of Neurology and Pediatrics, Emory University, Atlanta, Georgia (Loring)

Abstract

IMPORTANCE—Breastfeeding is known to have beneficial effects, but concern exists that breastfeeding during maternal antiepileptic drug (AED) therapy may be harmful. We previously noted no adverse effects of breastfeeding associated with AED use on IQ at age 3 years, but IQ at age 6 years is more predictive of school performance and adult abilities.

OBJECTIVES—To examine the effects of AED exposure via breastfeeding on cognitive functions at age 6 years.

DESIGN, SETTING, AND PARTICIPANTS—Prospective observational multicenter study of long-term neurodevelopmental effects of AED use. Pregnant women with epilepsy receiving monotherapy (ie, carbamazepine, lamotrigine, phenytoin, or valproate) were enrolled from October 14, 1999, through April 14, 2004, in the United States and the United Kingdom. At age 6 years, 181 children were assessed for whom we had both breastfeeding and IQ data. All mothers in this analysis continued taking the drug after delivery.

MAIN OUTCOMES AND MEASURES—Differential Ability Scales IQ was the primary outcome. Secondary measures included measures of verbal, nonverbal, memory, and executive functions. For our primary analysis, we used a linear regression model with IQ at age 6 years as the dependent variable, comparing children who breastfed with those who did not. Similar secondary analyses were performed for the other cognitive measures.

RESULTS—In total, 42.9% of children were breastfed a mean of 7.2 months. Breastfeeding rates

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Corresponding Author: Kimford J. Meador, MD, Department of Neurology and Neurological Sciences, Stanford University, 300 Pasteur Dr, Room A343, Stanford, CA, 94305-5235, (kmeador@stanford.edu).

Conflict of Interest Disclosures: Dr Meador reported serving on the editorial boards of Neurology, Behavior & Neurology, Epilepsy & Behavior, Epilepsy.com, and the Journal of Clinical Neurophysiology and on the professional advisory board for the Epilepsy Foundation; receiving travel support from sanofi-aventis; and receiving research support from GlaxoSmithKline, Eisai Inc, Marinus Pharmaceuticals Inc, Myriad Genetics Inc, NeuroPace Inc, Pfizer Inc, SAM Technology Inc, UCB Pharma, the National Institutes of Health (National Institute of Neurological Disorders and Stroke 2R01-NS38455 [principal investigator], 2U01-NS038455 [multi-principal investigator], and 1R01-NS076665 [consultant]), the Patient-Centered Outcomes Research Institute (527 [co-principal investigator]), and the Epilepsy Foundation. Dr Meador reported having consulted for the Epilepsy Study Consortium and receiving money from multiple pharmaceutical companies (in relation to his work for Eisai Inc, NeuroPace Inc, Novartis, Supernus, Upsher Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals). The funds for consulting for the Epilepsy Study Consortium were paid to Emory University. Dr Baker reported serving on a scientific advisory board for sanofi-aventis; serving on the editorial board of Epilepsy and Behavior; having received speaker honoraria from Eisai Inc, UCB Pharma, and Janssen; receiving research support from UCB Pharma, sanofi-aventis, Pfizer Inc, Epilepsy Research United Kingdom, Medical Research Council, and Epilepsy Action United Kingdom; and having served as an expert witness in litigation related to neurodevelopmental effects of antiepileptic drugs. Dr Browning reported receiving research support from the National Institutes of Health, including National Institute of Neurological Disorders and Stroke R01-NS050659 (statistician and data center principal investigator), grant 2U01NS038455-11A1, Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs grant, National Institute of Neurological Disorders and Stroke and National Institute of Child Health and Human Development contract N01-A1-80013, and the Statistical and Data Coordinating Center Clinical Research in Infectious Disease contract for Division of Microbiology and Infectious Diseases/National Institute of Allergy and Infectious Diseases HHSN272200800013C. Dr Cohen reported serving on the editorial board of Developmental Neuropsychology and receiving royalties from the publication of Children's Memory Scale (Psychological Corporation, 1997). Dr Bromley reported receiving lecture fees from sanofi-aventis (2 occasions), receiving conference travel support from UCB Pharma, and providing expert testimony pertaining to fetal anticonvulsant syndrome. Dr Clayton-Smith is the journal editor for Clinical Dysmorphology and reported having served as an expert witness in litigation related to neurodevelopmental effects of antiepileptic drugs. Dr Kalayjian reported receiving funding from the National Institutes of Health. Dr Kanner is a member of the data safety board for Vertex Laboratories and reported having served as a consultant for NeuroPace Inc. Dr Liporace reported receiving royalties from the publication of Crash Course Neurology (Elsevier, 2006) and having served on speakers' bureaus for and received speaker honoraria from UCB Pharma and GlaxoSmithKline. Dr Pennell reported receiving research funding toward salary support from the Epilepsy Therapy Project, the Epilepsy Foundation, and the National Institutes of Health; receiving travel support and honoraria from the American Epilepsy Society and the American Academy of Neurology; and receiving travel support from the Tbilisi State Medical University and the Indian Academy of Neurology. She also reported serving as a volunteer member of the board of directors of the American Epilepsy Society and of the professional advisory board of the Epilepsy Foundation. Dr Privitera reported serving on scientific advisory boards or as a consultant on the data and safety monitoring boards for Upsher Smith Laboratories, GlaxoSmithKline, Lilly, and Astellas; receiving funding for travel and speaker honoraria from UCB Pharma; serving on speakers' bureau for UCB Pharma; and receiving research support from UCB Pharma, Neuren, Eisai Inc, the National Institutes of Health (K23 NS052468 [co-mentor]), the American Epilepsy Society, the Food and Drug Administration, and the Shor Foundation for Epilepsy Research. Dr Loring reported serving on scientific advisory boards for the Epilepsy Foundation, serving as an associate editor for Epilepsia and is on the editorial board of Neuropsychology Review and Epilepsy Research, serving as a consultant for NeuroPace Inc, receiving royalties from the publication of the fourth edition of Neuropsychological Assessment (Oxford University Press, 2004) and INS Dictionary of Neuropsychology (Oxford University Press, 1999), estimating that 50% of his clinical effort involves neuropsychological testing, and receiving research support from the National Institutes of Health (National Institute of Neurological Disorders and Stroke R01038455 [coinvestigator] and R01 NS035929 [coinvestigator]) and the Patient-Centered Outcomes Research Institute (527 [principal investigator]). No other disclosures were reported.

Group Information: The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group investigators are listed at the end of this article.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. A National Institutes of Health-appointed data and safety monitoring board oversaw the study conduct.

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Author Contributions: Drs Meador and Browning had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Meador, Baker, Loring. *Acquisition, analysis, or interpretation of data:* All authors.

Drafting of the manuscript: Meador, Browning.

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and duration did not differ across drug groups. The IQ at age 6 years was related to drug group ($P < .001$ [adjusted IQ worse by 7–13 IQ points for valproate compared to other drugs]), drug dosage (regression coefficient, -0.1 ; 95% CI, -0.2 to 0.0 ; $P = .01$ [higher dosage worse]), maternal IQ (regression coefficient, 0.2 ; 95% CI, 0.0 to 0.4 ; $P = .01$ [higher child IQ with higher maternal IQ]), periconception folate use (adjusted IQ 6 [95% CI, 2–10] points higher for folate, $P = .005$), and breastfeeding (adjusted IQ 4 [95% CI, 0–8] points higher for breastfeeding, $P = .045$). For the other cognitive domains, only verbal abilities differed between the breastfed and nonbreastfed groups (adjusted verbal index 4 [95% CI, 0–7] points higher for breastfed children, $P = .03$).

CONCLUSIONS AND RELEVANCE—No adverse effects of AED exposure via breast milk were observed at age 6 years, consistent with another recent study at age 3 years. In our study, breastfed children exhibited higher IQ and enhanced verbal abilities. Additional studies are needed to fully delineate the effects of all AEDs.

TRIAL REGISTRATION—clinicaltrials.gov Identifier: NCT00021866

Similar to alcohol, some antiepileptic drugs (AEDs) can cause widespread neuronal apoptosis in the immature animal brain.^{1–8} This effect is dose dependent, occurs at therapeutically relevant blood levels, and requires only brief exposure. The associated behavioral deficits in animals may be due more to dysfunction in the surviving neurons than to the loss of neurons.⁹ Consistent with these findings in animals, some AEDs have been associated with reduced cognitive abilities in children exposed in utero.^{10–14} Susceptibility of the immature brain to AED-induced apoptosis likely extends beyond birth, so concern has been raised that breastfeeding during maternal AED therapy might be harmful to the child. In contrast, known positive effects of breastfeeding exist for the child and mother.¹⁵ Therefore, a clinical dilemma presents as to the relative benefits and risks of breastfeeding during AED therapy. No animal data to date directly address this issue. In an ongoing prospective investigation of neurodevelopmental effects of AEDs on cognitive outcomes in children of mothers with epilepsy, the preliminary results at age 3 years found no difference in IQ for children who breastfed vs those who did not.¹⁶ However, IQ at age 6 years is more predictive of school performance and adult abilities.¹⁷ Furthermore, additional cognitive domains can be assessed at age 6 years vs at age 3 years. So, we examined cognitive outcomes in our cohort at age 6 years.

Methods

Standard Protocol Approvals and Patient Consents

Institutional review boards at each center approved the study. Written informed consent was obtained before participant enrollment.

Design

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective observational study examining possible behavioral teratogenesis of AED use. We enrolled pregnant women with epilepsy who were receiving AED monotherapy (ie, carbamazepine, lamotrigine, phenytoin, or valproate) from October 14, 1999, through April 14, 2004, across

25 epilepsy centers in the United States and the United Kingdom. We recently reported our primary outcome on differential effects of fetal AED exposure on IQ at age 6 years,¹⁴ but that publication did not directly contrast breastfed and nonbreastfed children. Herein, we reexamine the hypothesis that breast-feeding during AED therapy is detrimental to the child's cognitive development.

Participants

Pregnant women with epilepsy taking carbamazepine, lamotrigine, phenytoin, or valproate monotherapy were enrolled. These 4 AED monotherapies were the most frequently used during the enrollment period. Other AEDs were not included because of insufficient numbers. Polytherapy was not included because of its association with poorer outcomes.¹² A nonexposed control group was not included at the direction of a National Institutes of Health review panel. Mothers with an IQ of less than 70 were excluded to avoid floor effects and because maternal IQ is the major predictor of child IQ in population investigations.¹⁷ Other exclusion criteria included positive syphilis or human immunodeficiency virus serology, progressive cerebral disease, other major disease (eg, diabetes mellitus), exposure to teratogenic agents other than AEDs, poor AED adherence, drug abuse in the prior year, or drug abuse sequelae.

Procedures

Information was collected on the following potentially confounding variables: maternal IQ, age, educational level, employment, race/ethnicity (self-report, obtained to assess potential confounding effects on outcomes), seizure (or epilepsy) types and frequency, AED dosages, adherence, socioeconomic status,¹⁸ United Kingdom vs United States site, periconception folate use, unwanted pregnancy, abnormalities or complications in the present pregnancy or prior pregnancies, enrollment and birth gestational age, birth weight, breastfeeding, childhood medical diseases, and the use of alcohol, tobacco, or other drugs during pregnancy. Children were classified as breastfed if they were breastfeeding at the time of the 3-month follow-up telephone call after delivery. Cognitive outcomes were evaluated by assessors (blinded to AED) using Differential Ability Scales¹⁹ (conducted at age 71–87 months); standardized scores were calculated. Separate investigations with similar designs in the United States and the United Kingdom were merged after initiation. Maternal IQs were determined by different measures because of the later merger, including the Test of Nonverbal Intelligence²⁰ in 265 mothers, Wechsler Abbreviated Scale of Intelligence²¹ in 20 mothers, and National Adult Reading Test²² in 17 mothers. Training and monitoring of neuropsychological evaluations were conducted to assure quality and consistency. Face-to-face training on all neuropsychological test batteries was performed annually. Each assessor was required to identify errors in a videotaped test session and provide appropriate correction for errors in administration and scoring. In addition, assessors submitted their own videotape and record forms using each test instrument to the neuropsychology core directors (M.J.C. and D.W.L.) for review, feedback, and approval. If assessors failed, they submitted additional video assessment for approval before testing children in the study.

Statistical Analysis

The primary analysis in this substudy included 181 children for whom data were available on both cognitive assessment at age 6 years and breastfeeding. Two children with complete data were excluded from this sample because their mothers switched AEDs or stopped using AEDs when breastfeeding. In the primary analysis, the breastfed and nonbreastfed groups were compared across all AEDs with respect to child cognitive outcomes at age 6 years. Secondary analyses examined the following: (1) effects of breastfeeding within each AED group, (2) the sensitivity of the results to baseline differences in covariates, and (3) the sensitivity of the results to missing data. Power was 95% to detect a 0.5-SD IQ effect in the combined AED analysis but was inadequate within groups. Analyses were performed at the NEAD Data and Statistical Center using statistical software (SAS version 9.2; SAS Institute Inc).

Linear regression models were used to examine breastfed vs nonbreastfed group differences in IQ adjusting for AED group, maternal IQ, standardized AED dosage, and periconception folate use. These covariates were significantly related to IQ outcomes at age 6 years in this analysis.¹⁴ Linear models also included propensity scores^{22,23} as a covariate (discussed in more detail in the paragraph that follows). A non-parametric Kruskal-Wallis test was used to compare duration of breastfeeding across AED groups.

Because the women were not randomized to breastfeeding or to specific AEDs in this observational study, baseline differences between AED groups might obscure negative effects of AEDs taken during breastfeeding. Propensity score methods are well-accepted tools to examine this possibility.^{24,25} Propensity scores are predicted probabilities of receiving a treatment (or, in this case, being breastfed) based on baseline covariates. Individuals with equal values of the propensity score are similar with respect to baseline characteristics. Propensity scores were estimated using predicted probabilities from a logistic regression model with breastfeeding status (yes or no) as the outcome. Variables related to breastfeeding were predictors in the propensity score model, along with variables significantly related to IQ at age 6 years. The predictors in the propensity score model included AED group, dosage, maternal IQ, maternal and gestational age, periconception folate use, tobacco use during pregnancy, educational level, socioeconomic status, and unwanted pregnancy (yes or no). When the propensity score is included as a covariate in the linear model, breastfed or nonbreastfed least squares means can be interpreted as expected means for each group at the same baseline covariate values. Propensity scores only consider measured baseline covariates. The sensitivity of the results to unmeasured baseline covariates was also assessed.^{26,27}

To investigate the sensitivity of the primary results to missing data (missing outcome at age 6 years or missing breastfeeding data), analyses were also conducted using the intent-to-treat sample (311 live births, including 6 twin pairs). To account for missing data, a third breastfeeding category was created for breastfeeding data missing to compare with the breastfed and nonbreastfed groups. One child was excluded because the mother had missing data on maternal IQ. Two children were excluded from the analysis because the mother stopped using AEDs or switched AEDs when breastfeeding, resulting in an analysis sample size of 308. Data were available for breastfeeding in 249 (80.8%). Outcomes at age 6 years

were missing in 85 (27.6%). Markov chain Monte Carlo methods were used in secondary analyses to impute missing outcomes at age 6 years from available outcomes at ages 2, 3, and 4½ years and baseline variables related to outcome or missingness.^{28–30} Baseline variables in the imputation model included AED, dosage, maternal IQ, educational level, employment status and age, gestational age at delivery, periconception folate use, convulsions during pregnancy, socioeconomic status, unwanted pregnancy (yes or no), and United States or United Kingdom site. Least squares mean IQs were estimated for the breastfed and nonbreastfed groups adjusting for maternal IQ, AED group, dosage, periconception folate use, and propensity score. Standard errors and 95% CIs of all estimates incorporated imputation uncertainty.

To assess whether the results were similar across all ages when IQ was measured, a repeated-measures model was estimated using all available data at ages 2, 3, 4½, and 6 years. This model incorporated within-subject correlations over time and included child age, along with breastfeeding status, maternal IQ, AED group, periconception folate use, and standardized dosage as covariates. At each age, the adjusted means were compared for breastfed vs nonbreastfed children.

Results

The primary analysis included 177 mothers and 181 children (4 sets of twins). Baseline characteristics of the breastfed and nonbreastfed groups and differences between groups are summarized in Table 1. Across AEDs, 42.9% (95% CI, 35.8%–50.7%) of the children were breastfed for a mean duration of 7.2 months (95% CI, 6.2–8.3 months; range, 3–24 months). Breastfeeding rates did not differ across AEDs ($P = .37$, Fisher exact test). The means of breastfeeding rates of children for each AED were 48.9% (95% CI, 34.1%–63.9%) for carbamazepine, 44.3% (95% CI, 31.6%–57.6%) for lamotrigine, 46.0% (95% CI, 29.5%–63.1%) for phenytoin, and 30.6% (95% CI, 16.4%–48.1%) for valproate. Breastfeeding duration did not differ across AEDs ($P = .86$, nonparametric Kruskal-Wallis test). The mean breastfeeding durations were 6.9 months (95% CI, 5.1–8.7 months) for carbamazepine, 7.8 months (95% CI, 5.9–9.7 months) for lamotrigine, 6.5 months (95% CI, 5.0–8.1 months) for phenytoin, and 7.8 months (95% CI, 3.0–12.6 months) for valproate. The mean (SD) AED dosages during pregnancy were 803 (371) mg/d for carbamazepine, 508 (244) mg/d for lamotrigine, 393 (133) mg/d for phenytoin, and 1160 (714) mg/d for valproate. Standardized AED dosages are listed in Table 1. Pregnancy dosages did not differ for breastfed vs nonbreastfed groups for each AED (eTable 1 in the Supplement).

The IQ at age 6 years was related to maternal IQ (regression coefficient, 0.2; 95% CI, 0.0 to 0.4; $P = .01$), drug group ($P < .001$), drug dosage (regression coefficient, -0.1 ; 95% CI, -0.2 to 0.0 ; $P = .01$), periconception folate use (regression coefficient, 5.7; 95% CI, 1.7 to 9.7; $P = .005$), and breastfeeding (regression coefficient, 4.1; 95% CI, 0.1 to 8.1; $P = .045$) (Table 2). As shown in our previous report,¹⁴ higher maternal IQ was associated with higher child IQ, fetal valproate exposure was associated with lower child IQ, higher AED dosage was associated with lower IQ (this effect was driven by valproate), and periconception folate use was associated with higher IQ (adjusted IQ 6 points [95% CI, 2–10] higher for the folate group).

Overall, adjusted IQ was higher by 4 points for children who were breastfed vs those who were not. Table 3 lists the adjusted mean IQs (95% CIs) for the breastfed and nonbreastfed groups across all AEDs and for each AED. For the other cognitive domains, only verbal abilities differed across the breastfed and nonbreastfed groups ($P = .03$), with a higher score for breastfed children. The adjusted means (95% CIs) of the different cognitive domains across all AEDs are listed in Table 4 and are summarized for each individual AED in eTable 2 in the Supplement.

The propensity score analysis suggests that the results are not due to differences in baseline variables related to child IQ or breastfeeding status (Table 2). The sensitivity analysis in eTable 3 in the Supplement suggests that the results are not sensitive to unmeasured covariates. Missing data for IQ at age 6 years and for breastfeeding for each AED group are summarized in eTable 4 and eTable 5 in the Supplement. In the intent-to-treat sample, which included 308 of the originally enrolled children, missing outcomes were imputed, and a third breastfeeding category was created for breastfeeding data missing. The results are similar to those of the primary analysis. The intent-to-treat adjusted mean IQs are 107 (95% CI, 105–110) for the breastfed group, 103 (95% CI, 101–105) for the nonbreastfed group, and 102 (95% CI, 98–106) for the group with breast-feeding data missing. eTable 6 in the Supplement summarizes the repeated-measures model, with the adjusted means at each age and overall. The pattern of higher means for the breastfed group persists over time in the sample of children with testing data available from at least one time point. The analyses examining the sensitivity of the results to missing data and the repeated-measures model over time suggest that the results cannot be explained by incomplete data at age 6 years.

Discussion

The present study found no adverse cognitive effects of breastfeeding during maternal AED therapy on cognitive outcomes in children who were previously exposed to AEDs during their mother's pregnancy. This is similar to the results from this cohort at age 3 years¹⁶ and to another recent study³¹ with a different cohort at age 3 years. Furthermore, our results at age 6 years show higher IQ (by 4 points) and enhanced verbal abilities (by 4 points) in breastfed children, even after adjustment for other factors related to child cognitive outcomes (eg, maternal IQ). These positive breastfeeding effects are consistent with 3 recent large prospective cohort studies^{32–34} in the general population. Although the effects of breastfeeding on cognition remain controversial,^{35,36} our results add to other evidence supporting a causal relationship of breastfeeding with improved cognitive abilities.³⁷

No controversy exists on other beneficial effects of breastfeeding.¹⁵ In children, breastfeeding is associated with a reduced risk of severe lower respiratory tract infections, atopic dermatitis, asthma, acute otitis media, nonspecific gastroenteritis, obesity, type 1 and 2 diabetes mellitus, childhood leukemia, sudden infant death syndrome, and necrotizing enterocolitis. In mothers, breastfeeding is associated with a reduced risk for type 2 diabetes mellitus, breast cancer, ovarian cancer, and maternal postpartum depression.^{15,38} Therefore, these other positive effects would suggest that, even if breastfeeding does not enhance the child's cognition, it would be beneficial in the setting of epilepsy as long as no adverse cognitive effects of AED exposure present via breast milk.

Although strong evidence exists that certain AEDs can produce neuronal apoptosis in immature animal brains¹⁻⁸ and that fetal exposure to some AEDs is associated with reduced cognitive abilities in children,¹⁰⁻¹⁴ potential reasons explain the apparent disparity in fetal vs breastfeeding AED exposures seen in our study. The AED-induced apoptosis in the immature brain is dose dependent¹⁻⁸ and ultimately related to the actual drug level in the fetus or infant. Furthermore, AED-induced apoptosis requires only a single exposure,¹⁻⁹ so it is possible that the adverse effects may be related more to the peak AED level than to the total exposure.³⁹ The AED level in the child from breastfeeding is dependent on multiple factors, including the amount of AED excreted into breast milk, the amount of breast milk consumed by the infant, the amount of AED absorbed, and the clearance of the AED by the infant.⁴⁰ Therefore, the amount of AED in breast milk may not be directly related to the AED serum levels in the infant. Although the data are incomplete, estimates of AED exposure from breast milk suggest that it is low for many AEDs.^{41,42} Data on AED serum levels in the breastfeeding child are sparse except for lamotrigine.^{41,42} In a study⁴² of 30 mother-child pairs, infant plasma concentrations were 18.3% of maternal plasma concentrations. Future studies need to assess AED levels in breastfed children to demonstrate that the actual AED level is very low or to suggest that the benefits of breastfeeding counteract the potential harm of breastfeeding AED exposure.

The proposed benefits of breastfeeding on newborn cognitive development³⁷ could offset potential deleterious effects of continued AED exposure, but the fact that the observed IQs in our study for the breastfeeding group were comparable or greater than those for the general population would argue against this potential explanation. The exact window for susceptibility of the immature brain to the adverse effects of AEDs is unknown. Therefore, it is possible that the adverse AED effects might be greater on the fetal brain than on the neonatal brain.

Consistent with our prior study,¹⁴ IQ at age 6 years in children of women with epilepsy is related to maternal IQ, periconception folate use, and type or dosage of AED exposure. Fetal valproate exposure was associated with lower IQ in a dose-dependent manner. As recommended by the American Academy of Neurology, valproate should be avoided if possible during pregnancy to decrease major congenital malformations and cognitive impairments.¹²

Our study has several strengths and limitations. Strengths include the prospective design, blinded cognitive assessments using standardized measures, and detailed monitoring of multiple potential confounding factors. Limitations include a small sample size, the loss of enrolled participants to analysis, an absence of data on the concentrations in breast milk or in children's serum, lack of randomization, an unexposed control group, details to fully quantify the amount of breastfeeding, and AED dosage data during breastfeeding. Furthermore, the potential deleterious effects of AED exposure via breast milk in newborns who have not been previously exposed in utero are not addressed by our study. Because the NEAD study is an observational investigation, the effects of breastfeeding during AED therapy might be confounded by differences in baseline characteristics between the breastfed and nonbreastfed groups. However, analyses adjusting for baseline characteristics, including

the propensity score subgroup analyses, did not alter our findings. Nevertheless, residual confounding effects cannot be completely ruled out.

Additional studies are needed to confirm our findings and extend investigations to other AEDs and to AED polytherapy. Furthermore, future studies should include direct measures of AED exposures via breast milk (ie, AED blood levels in the child).

Investigators in our study have commonly encountered women in their epilepsy clinics who have been told that they should not breastfeed because it is unsafe for the child. Recently, a woman with focal epilepsy was first encountered in the postpartum period by one of us (P.B.P.). After delivery, the mother began to breastfeed her newborn but was approached the day after delivery by the pediatrician and nursing team, including a lactation nurse, who told her that it was unsafe to breastfeed, which was then confirmed by a neurology consultation. The woman chose to continue to breastfeed and was reported by the medical team to the Department of Children and Families for suspected child abuse or neglect. Ultimately, the case was closed by the department after a home visit and additional legal steps to clear the mother's personal record. She continued to almost exclusively breastfeed her daughter; examination at age 6 months revealed a healthy infant with normal growth and development. Although general population data supporting the multiple positive effects of breastfeeding are strong, clinical data to support theoretical risks of breastfeeding are nonexistent to date. Dogmatic clinical recommendations without an evidence base do not serve patients well.

Conclusions

Our study does not provide a final answer, but we recommend breastfeeding to mothers with epilepsy, informing them of the strength of evidence for risks and benefits. Our recommendation is based on the known positive effects of breastfeeding, the results of our study, an unsubstantiated speculative risk, and theoretical reasons why breastfeeding when taking AEDs would not offer additional risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Group Information

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group clinical site coinvestigators were David Labiner, MD, Arizona Health Sciences Center, Tucson; Jennifer Moon, PhD, Arizona Health Sciences Center, Tucson; Scott Sherman, MD, Arizona Health Sciences Center, Tucson; Cheryl Silver, PhD, University of Texas–Southwestern, Dallas; Alison Pack, MD, Columbia University, New York, New York; Joyce Echo, PhD, Columbia University, New York, New York; Kimford J. Meador, MD, Stanford University, Stanford, California; David W. Loring, PhD, Emory University, Atlanta, Georgia; Daniel Drane, PhD, Emory University, Atlanta, Georgia; Eugene Moore, BS, Emory University, Atlanta, Georgia (multisite coordinator); Sandra Helmers, MD, Emory University, Atlanta, Georgia; Gholam Motamedi, MD, Georgetown University, Washington, DC; Gregory Lee, PhD,

Georgia Regents University, Augusta; Morris J. Cohen, EdD, Georgia Regents University, Augusta; Page B. Pennell, MD, Brigham and Women's Hospital, Boston, Massachusetts; Edward Bromfield, MD, Brigham and Women's Hospital, Boston, Massachusetts (deceased); Katrina Boyer, PhD, Brigham and Women's Hospital, Boston, Massachusetts; Barbara Dworetzky, ScB, Brigham and Women's Hospital, Boston, Massachusetts; Andrew Cole, MD, Massachusetts General Hospital, Boston; Barbara Moir, MS, Henry Ford Hospital, Detroit, Michigan; Cynthia Harden, MD, Medical College of Cornell University, New York, New York; Tara Tamny-Young, PhD, Medical College of Cornell University, New York, New York; Patricia Penovich, MD, Minnesota Epilepsy Group, St Paul; Donna Minter, EdD, Minnesota Epilepsy Group, St Paul; Joyce D. Liporace, MD, Riddle Health Care, Media, Pennsylvania; Kathryn Wilcox, BS, Riddle Health Care, Media, Pennsylvania; Andres Kanner, MD, University of Miami, Miami, Florida; Michael N. Nelson, PhD, Rush University Medical Center, Chicago, Illinois; William Rosenfeld, MD, The Comprehensive Epilepsy Care Center for Children and Adults, St Louis, Missouri; Michelle Meyer, MEd, The Comprehensive Epilepsy Care Center for Children and Adults, St Louis, Missouri; Jill Clayton-Smith, MD, University of Manchester, Manchester, England; Rebecca L. Bromley, PhD, University of Manchester, Manchester, England; Usha Kini, MD, St Mary's Hospital, Manchester, England; Michael Privitera, MD, University of Cincinnati, Cincinnati, Ohio; David Ficker, MD, University of Cincinnati, Cincinnati, Ohio; Lyle Baade, PhD, University of Kansas School of Medicine–Wichita; Gus A. Baker, PhD, University of Liverpool, Merseyside, England; Alison Gummery, PhD, University of Liverpool, Merseyside, England; Rebecca Shalcross, PhD, University of Liverpool, Merseyside, England; Patricia Arena, PhD, University of Miami, Miami, Florida; Laura A. Kalayjian, MD, University of Southern California, Los Angeles; Christianne Heck, MD, University of Southern California, Los Angeles; Sonia Padilla, PsyD, University of Southern California, Los Angeles; John Miller, MD, University of Washington, Seattle; Gail Rosenbaum, BA, University of Washington, Seattle; Alan Wilensky, MD, University of Washington, Seattle; Maria Sam, MD, Wake Forest University, Winston-Salem, North Carolina; and Cormac O'Donovan, MD, Wake Forest University, Winston-Salem, North Carolina.

Executive Committee Coinvestigators

Gregory L. Holmes, MD, University of Vermont, Burlington; Maurice Druzin, MD, Stanford University, Stanford, California; Martha Morrell, MD, Stanford University, Stanford, California; Lorene Nelson, PhD, Stanford University, Stanford, California; Richard Finnell, PhD, Texas A&M University Health Science Center, Houston; Mark Yerby, MD, University of Oregon, Portland; Khosrow Adeli, PhD, University of Toronto, Toronto, Ontario, Canada; and Peter Wells, PharmD, University of Toronto, Toronto, Ontario, Canada.

Data and Statistical Center Coinvestigators (all with The EMMES Corporation, Rockville, Maryland)

Temperance Blalock, AA; Nancy Browning, PhD; Lisa Davis, BA; Linda Hendrickson; Dominic Ippolito, MS; Bernadette Jolles, MA; Meghan Kelly Kunchai, MPH; Hayley

Loblein, BS; Merin Mathew, MS; Ryan May, PhD; Kaitlyn Menard, BS; Chinh Ott, BS; Sarah Romano, MPH; Noble Shore, MS; Mark Wolff, PhD; Phyllis Zaia Renehan, BS; and Thad Zajdowicz, MD, MPH.

Table 1

Baseline Characteristics of 177 Mothers According to Breastfeeding Status for 181 Children With Data on Both Breastfeeding Status and IQ at Age 6 Years

Variable	Breastfed	Nonbreastfed	Mean Difference (95% CI)	P Value ^a
Mothers, No./total No. (%) ^b	76/177 (42.9)	101/177 (57.1)	Not applicable	.06
Maternal IQ, mean (95% CI)	105 (101 to 109)	95 (92 to 98)	10 (5 to 15)	<.001
Maternal age at delivery, mean (95% CI), y	31 (30 to 32)	30 (29 to 31)	2 (0 to 3)	.03
Standardized dosage, mean (95% CI) ^c	36 (32 to 40)	38 (34 to 43)	-2 (-8 to 4)	.46
Gestational age at delivery, mean (95% CI), wk	39 (39 to 39)	39 (38 to 39)	0 (0 to 1)	.44
Periconception folate use, No./total No. (%)	52/76 (68.4)	54/101 (53.5)	15.0% (0.6% to 29.2%)	.04
United Kingdom site, No./total No. (%)	15/76 (19.7)	34/101 (33.7)	-13.9% (-26.8% to -1.1%)	.04
Seizure or epilepsy type, No./total No. (%) ^d				
Localization related	44/76 (57.9)	65/101 (64.4)	-6.5% (-21.0% to 8.1%)	.36
Idiopathic generalized	22/76 (28.9)	29/101 (28.7)	0.2% (-13.3% to 13.7%)	
Generalized tonic-clonic seizures ^e	10/76 (13.2)	7/101 (6.9)	6.2% (-2.8% to 15.3%)	
Convulsions, No./total No. (%)				
None	60/69 (87.0)	70/94 (74.5)	12.5% (0.6% to 24.4%)	.14
>5 ^f	1/69 (1.4)	3/94 (3.2)	-1.7% (-6.3% to 2.8%)	
Maternal race/ethnicity, No./total No. (%)				
White	62/76 (81.6)	81/101 (80.2)	1.4% (-10.3% to 13.1%)	.13
Black	1/76 (1.3)	6/101 (5.9)	-4.6% (-9.9 to 0.7%)	
Hispanic	7/76 (9.2)	12/101 (11.9)	-2.7% (-11.7% to 6.4%)	
Other	6/76 (7.9)	2/101 (2.0)	5.9% (-0.7% to 12.6%)	

^a χ^2 Test of equal proportions for categorical variables; *t* test for continuous variables.

^b Number (percentage) by breastfeeding category; maternal racial/ethnic distributions were 81% white, 4% black, 11% Hispanic, and 5% other.

^c Mean dosage for pregnancy (see the Statistical Analysis subsection of the Methods section for a description of how dosages were standardized).

^d The 3 epilepsy types were localization related, idiopathic generalized, and generalized tonic-clonic seizures (unknown if partial or generalized). Maternal seizure types included 62% localization related (simple partial, complex partial, or secondary generalized tonic-clonic), 29% idiopathic generalized (absence, myoclonic, tonic-clonic, or tonic seizures with initial bilateral cerebral involvement as indicated by electroencephalogram or clinical syndrome), and 10% generalized tonic-clonic seizures (uncertain if partial or generalized). The focal epilepsies were 41% symptomatic and 59% cryptogenic. All generalized epilepsies were idiopathic (4% juvenile myoclonic, 6% absence, 20% positive family history but without an identified specific genetic abnormality, and 71% not otherwise classified).

^e Uncertain if focal or generalized.

^f In mothers without convulsions or with more than 5 convulsions during pregnancy; seizure frequency during pregnancy was unavailable for 14 mothers.

Table 2Results of the Primary Linear Regression Analysis With IQ at Age 6 Years as the Dependent Variable^a

Effect	F Score	df	Coefficient (95% CI)	P Value
Breastfeeding status	4.1	1	4.1 (0.1 to 8.1)	.045
AED group across 4 drugs	7.9	3	Not applicable	<.001
Maternal IQ	6.8	1	0.2 (0.0 to 0.4)	.01
Periconception folate use	8.1	1	5.7 (1.7 to 9.7)	.005
AED dosage	6.6	1	-0.1 (-0.2 to 0.0)	.01
Propensity score ^b	1.1	1	7.5 (-6.6 to 21.6)	.30

Abbreviation: AED, antiepileptic drug.

^aLinear regression models were used to examine breastfeeding effects adjusting for covariates. The goal was a parsimonious model in which all covariates were significant at the .05 level and a model that was not overfitted. To select covariates for inclusion in the model, we first relied on an approach that considered a priori hypotheses about clinical relevance. Breastfeeding status was included as the primary covariate of interest. Because specific AED, dosage, and maternal IQ were considered important covariates, we included these variables as predictors in the linear model, with child IQ as the outcome. Other covariates were added individually to the model and included if significant ($P < .05$) and not collinear with existing predictors. We inspected diagnostic plots to ensure that distributional assumptions of the models were met. An automated backward selection method confirmed our selection of covariates. Backward elimination started from the full model, including all possible covariates, which were deleted one by one based on a significance limit of .10. At each step, the covariate showing the smallest contribution was deleted based on the F score.

^bPropensity scores are predicted probabilities of receiving a treatment given baseline covariates.^{22,23} Individuals with the same propensity score values are considered balanced with respect to their observed covariates.

Table 3

Adjusted IQs at Age 6 Years Across Antiepileptic Drugs (AEDs) Comparing Breastfed vs Nonbreastfed Children^a

AED Group	IQ, Mean (95% CI)			P Value
	Breastfed	Nonbreastfed	Difference	
All AEDs	108 (105 to 111) (n = 78)	104 (101 to 106) (n = 103)	4 (0 to 8)	.04
Carbamazepine	107 (101 to 113) (n = 23)	105 (99 to 110) (n = 24)	2 (−6 to 11)	.61
Lamotrigine	113 (110 to 117) (n = 27)	110 (107 to 113) (n = 34)	3 (2 to 8)	.23
Phenytoin	104 (99 to 110) (n = 17)	108 (103 to 113) (n = 20)	−4 (−12 to 4)	.23
Valproate	106 (97 to 115) (n = 11)	94 (88 to 100) (n = 25)	12 (1 to 24)	.04

^a Adjusted for other significant factors in the model (ie, maternal IQ, AED group, AED dosage, periconception folate use, and breastfeeding) plus the propensity score. The following were not significant: socioeconomic status, educational level, race/ethnicity, seizure or epilepsy type, maternal age, number of convulsions (none vs >5), United Kingdom site, any use of alcohol during pregnancy, any use of tobacco during pregnancy, employment (at the time of enrollment), pregnancy complications, prior pregnancy complications, prior pregnancy birth defects, and whether the pregnancy was unwanted.

Table 4

Adjusted Cognitive Domain Indexes at Age 6 Years Across Antiepileptic Drugs (AEDs) Comparing Breastfed vs Nonbreastfed Children^a

Cognitive Domain	Cognitive Domain Index, Mean (95% CI)			P Value
	Breastfed	Nonbreastfed	Difference	
Verbal	105 (103 to 108) (n = 79)	102 (100 to 104) (n = 102)	4 (0 to 7)	.03
Nonverbal	105 (103 to 108) (n = 79)	104 (102 to 106) (n = 102)	2 (-1 to 5)	.30
Memory	103 (99 to 107) (n = 78)	100 (96 to 104) (n = 96)	3 (-2 to 9)	.27
Executive function	105 (102 to 107) (n = 78)	104 (101 to 106) (n = 99)	1 (-2 to 4)	.53
Parent BRIEF	103 (101 to 106) (n = 68)	101 (99 to 104) (n = 89)	2 (-2 to 6)	.29

Abbreviation: BRIEF, Behavior Rating Inventory of Executive Function.

^a Adjusted for other significant factors in the model (ie, maternal IQ, AED group, AED dosage, periconception folate use, and breastfeeding).